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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,234	02/18/2004	Michael A. Kuzyk	4616-67958	5234

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KLARQUIST SPARKMAN, LLP
121 SW SALMON STREET
SUITE 1600
PORTLAND, OR 97204

EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 09/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/782,234	KUZYK ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *1-3 and 7-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-6,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence alignment*.

FINAL ACTION

1. This Office Action is responsive to Applicant's amendment and response filed June 24, 2005. Claims 4-6 have been amended. Claims 13 and 14 have been added. Claims 1-3 and 7-12 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

2. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

Objections/Rejections Withdrawn

3. In view of Applicant's amendment the following rejections are withdrawn.

a) objection to the specification, page 2, paragraph 3.
b) objection to the specification, page 2, paragraph 4.
c) Rejection of claims 4-6 under 35 U. S.C. 112, second paragraph, page 9, paragraph 6 of the previous Office action
d) Rejection of claims 4-6 under 35 U. S.C. 102(b), pages 9-11, paragraph 7 of the previous Office action.

Rejections Maintained

4. The rejection under 35 U.S.C. 112, first paragraph is maintained for claims 4-6 and newly submitted claims 13 and 14 for the reasons set forth on pages 4-8 paragraph 5 of the previous Office Action.

The rejection was on the grounds that the claims are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vaccine comprising an immunogenic amount of a protein of 16 kDa as determined by SDS PAGE, said protein comprising the amino acid sequence as set forth in SEQ ID NO:2 does not reasonably provide enablement for a vaccine comprising an immunogenic amount of a protein of 16 kDa as determined by SDS PAGE, said protein

comprising an amino acid sequence that is a variant or fragment of SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches that the term "variant" is defined as any molecule having amino acid substitutions, deletions, and/or insertions provided that the final construct possesses the desired ability of OspA" (page 17). The specification has failed to provide a structure for the variants of the 16 kDa outer surface lipoprotein (SEQ ID NO:2). The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the protein's structure relates to function. However, the problem of the prediction of protein's structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polynucleotide and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such protein.

Thomas E. Creighton, in his book, *"Proteins: Structures and Molecular Properties, 1984"*, (page 315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a proline residue, which must distort the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book *"Protein Structure: A Practical Approach, 1989; pages 184-186"* teaches that present day site directed mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as introducing deletions and insertions". The reference goes on to teach that it is difficult to

know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in *"Protein Stability and Stabilization through Protein Engineering, 1991"* (chapter 7, page 197, second paragraph) adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

The claims of the instant application are not only drawn to a vaccine comprising a 16 kDa protein but are also drawn to a vaccine comprising fragments of the 16 kDa protein. There is no guidance provided in the specification as how one would begin to choose "fragments of the 16 kDa protein". The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does not disclose the following:

- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of sequence(s) which can be predictably modified and which regions are critical;
- what fragments can be made which the retain the biological activity if the intact protein; and
- the specification provides essentially no guidance as to which of the essentially infinite possible choice is likely to be successful.

Factors to be considered in determining whether undue experimentation is required are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other proteins having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use proteins that are variants or fragments of the 16 kDa outer surface lipoprotein of *Piscirickettsia salmonis* (OspA) in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The specification has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the amino acid's structure and still maintain activity is unpredictable and the experimentation left those skilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v Chugai

Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S. P.Q. 546(Bd. Pat=. App & int. 1986).

Applicant urges that they have amended the claims so that they no longer recite the use of variants or fragments.

Applicant's arguments filed June 24, 2005 have been fully considered but they are not persuasive. The claims as currently amended recite fragments of SEQ ID NO:2 to be used in the claimed vaccines. For example, claim 4 recites "a vaccine comprising an isolated protein of 16 kDa as determined by SDS PAGE, said protein comprising an amino acid sequence of one of SEQ ID No:2...". Therefore, the claims recite amino acid sequences that are less than the full-length of SEQ ID NO:2. Thus, the rejection set forth under 35 U.S.C. 112, first paragraph is maintained.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 102

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

5. Claims 4, 6 and newly submitted claim 14 are rejected under 35 U.S.C. 102(b) as anticipated by Barnes et al *(Diseases of Aquatic Organisms, Vol. 33:33-41, 1998).*

Claims 4, 6 and 14 are drawn to a vaccine comprising an isolated protein of 16 kDa as determined by SDS PAGE, said protein comprising an amino acid sequence of one of SEQ ID No:2, SEQ ID NO:4, or SEQ ID NO:6 for protecting a poikilothermic fish against infection by the bacterial pathogen *Piscirickettsia salmonis.*

Barnes et al teach a composition comprising a 56, 30 and 20kDa antigen from *Piscirickettsia salmonis* and distilled water (see the Abstract and page 35). Therefore, the prior art teach a composition comprising a 16 kDa protein. Barnes et al teach purified *P. salmonis* using density gradient centrifugation (pages 34-35). Therefore, the prior art teaches *Piscirickettsia salmonis* antigens that have been isolated. The amino acid sequence as is set forth in SEQ ID NO:2 would be inherent in the teachings of the prior art. The claim limitation "vaccine" is being viewed as a limitation of intended use. It should be remembered that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

Since the Office does not have the facilities for examining and comparing applicant's vaccine with the vaccine of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the vaccine of the prior art does not possess the same material structural and functional characteristics of the claimed vaccine). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

6. Claims 4, 6 and newly submitted claims 13-14 are rejected under 35 U.S.C. 102(e) as anticipated by Rubenfield et al *(US Patent No. 6,551,795 filed April 22, 2003).*

Claims 4, 6 and 13-14 are drawn to a vaccine comprising an isolated protein of 16 kDa as determined by SDS PAGE, said protein comprising an amino acid sequence of one of SEQ ID No:2, SEQ ID NO:4, or SEQ ID NO:6 for protecting a poikilothermic fish against infection by the bacterial pathogen *Piscirickettsia salmonis.*

Rubenfield et al teach vaccine compositions comprising an amino acid sequence of SEQ ID NO: 2. See attached sequence alignment. Rubenfield et al teach that the compositions of the invention may include suitable adjuvants (column 39). Rubenfield et al teach that polypeptides of the invention can be fused to other amino acid sequences which would include recombinant fusion polypeptides (column 6). The claim limitation "for protecting a poikilothermic fish against infection by the bacterial pathogen *Piscirickettsia salmonis*" is being viewed as a limitation of intended use.

Since the Office does not have the facilities for examining and comparing applicant's vaccine with the vaccine of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the vaccine of the prior art does not possess the same material structural and functional characteristics of the claimed vaccine). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 4-6 and 13-14 are rejected under 35 U.S.C. 103(a) unpatentable over Rubenfield et al *(US Patent No. 6,551,795 filed April 22, 2003)* in view of Mond et al *(WO99/47168 published September 23, 1999).*

Claims 4-6 and 13-14 are drawn to a vaccine comprising an isolated protein of 16 kDa as determined by SDS PAGE, said protein comprising an amino acid sequence of one of SEQ ID No:2, SEQ ID NO:4, or SEQ ID NO:6 for protecting a poikilothermic fish against infection by the bacterial pathogen *Piscirickettsia salmonis* wherein the isolated polypeptide is lapidated.

Rubenfield et al teach vaccine compositions comprising an amino acid sequence of SEQ ID NO: 2. See sequence alignment attached. Rubenfield et al teach that the compositions of the invention may include suitable adjuvants (column 39). Rubenfield et al teach that polypeptides of the invention can be fused to other amino acids sequences which would include recombinant fusion polypeptides (column 6). The claim limitation "for protecting a poikilothermic fish against infection by the bacterial pathogen *Piscirickettsia salmonis*" is being viewed as a limitation of intended use.

Rubenfield et al do not teach lipidated polypeptides.

Mond et al teach polypeptides conjugated to lipids or a lipid-containing moiety to promote a vigorous immune response to Type-2 T-cell independent antigens (see the Abstract). Mond et al teach that the lipid or lipid-containing moiety can be synthetic or derived from prokaryotic or eukaryotic sources (pages 8-9). Mond et al teach that a preferred microbial lipid is the lipoprotein OspA (page 9).Mond et al suggest that the conjugation of lipids or lipid-containing moieties to polypeptides may be successful in stimulating an immune response in immunocompromised patients such as the elderly, neonates and patients infected with HIV and other immunosuppressive pathogens (page 9.

It would be *prima facie* obvious at the time the invention was made to conjugate the polypeptides as taught by Rubenfield et al to the lipids or lipid moieties of Mond et al because Mond et al teach that polypeptides conjugated to lipids or a lipid-containing moiety promote a vigorous immune response to Type-2 T-cell independent antigens. Additionally, Rubenfield et al teach that the polypeptides of the invention can be modified using any protein modification (column 28). It would be expected barring evidence to the contrary, that the conjugation of the polypeptides of Rubenfield et al would be effective in promoting a Type-2, T-cell independent response when administered to a subject in a vaccine formulation.

Status of Claims

8. No claims allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

10. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
September 12, 2005

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Please mail W/ Office action

AA
PI Rubenfield MJ, Nolling J, Deloughery C, Bush D;
XX

Query Match 15.4%; Score 128.5; DB 7; Length 192;
Best Local Similarity 34.8%; Pred. No. 4.4e-05;
Matches 32; Conservative 13; Mismatches 28; Indels 19; Gaps 2;

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Qy         28 QEVGAATGAVVGGVAGQLFGKGSGRVAMAIGGAVLGGLIGSKIGQSMDQQDKI------- 80
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Db        140 STVHDSSEKVVGYDVKYMLDGKAGQIRMERDP 171
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